CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-064

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA:	21-064
Priority Classification:	S
Trade Name:	Definity™
Generic Name:	Perflutren
Sponsor:	Dupont Pharmaceuticals Company
Indications:	Ultrasound contrast agent for Echocardiography
Reviewing Statistician:	Mahboob Sobhan, Ph.D., HFD-715
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1.0 BACKGROUND

This NDA pertains to safety and efficacy data to support *Definity™*, a contrast-enhancing agent to be used in conjunction with echocardiography . Diagnostic echocardiography is a safe, non-invasive, and widely used imaging technique but often good image quality is limited to few patients and another imaging test is needed to confirm or rule out a diagnosis.

Definity™ is a new microbubble contrast agent designed to enhance echogenecity in echocardiographic in order to improve diagnosis. Based on data from several studies, the sponsor claims that this agent, specifically, (i) improves the visualization of cardiac ventricular chambers and endocardial borders in suspected cardiac patients

This review will focus on trial design and efficacy results for the pivotal studies. Specifically, this review will address the appropriateness of the endpoints used to support the purported objective(s), examine the consistency of the efficacy results across studies by performing independent analysis using sponsor's data, and evaluate the strength and weaknesses of the findings in light of the design employed. Safety consideration will be addressed in Medical Officers review.

1.1. Proposed Indication(s)

The sponsor proposes the following as the indications:

> **Cardiac:** *Definity™* is indicated for contrast-enhanced ultrasound imaging of cardiac structures (ventricular chambers and endocardial borders)

1.2 Summary of Pivotal Trials

To support the indications outlined above the submission consisted of 17 trials (six pivotal trials, one dose-ranging study, two other supportive trials, 3 clinical pharmacology trials, and 5 safety trials). Table 1 shows the summary of six pivotal trials to support cardiac indications.

For cardiac indication, two trials (DMP-004 and –005) provide data to support the cardiac structure (ventricular chambers and endocardial borders),

An additional trial (DMP-017) was conducted to compare the ability of DMP-115, when administered as an infusion vs. slow bolus, in cavity enhancement. The result of this trial would be found in MO's review. Table 1.2 summarizes the main features of these trials.

Table 1.2
Summary of Pivotal Studies

Indication	Study #	Total N	Tx. Groups	Design	Study Endpoints
Cardiology	DMP 115-004	87	Placebo, DMP 5 or 10 μL/kg	R, DB, Multicenter	• LV cavity enhancement • Endocardial Border Delineation • Videodensitometric Measurements
	DMP 115-005	124	Placebo, DMP 5 or 10 μL/kg	R, DB, Multicenter	• LV cavity enhancement • Endocardial Border Delineation • Videodensitometric Measurements
	DMP 115-006	67	2 IV bolus of DMP 10 μL/kg	Open-label, Multicenter	• Wall motion, EBD
	DMP 115-007	59	2 IV bolus of DMP 10 μL/kg	Open-label, Multicenter	• Wall motion, EBD

R: Randomized, DB: Double-blind, SB: Single-blind.

2.0 EVALUATION OF CARDIOLOGY INDICATION

2.1 Placebo-controlled Trials (Cardiac Structure)

2.1.A Study Design and Procedures

Design: Cardiac structure trials (DMP-004 and -005) were randomized, double-blind, placebo-controlled where patients were assigned to receive either two single bolus of IV dose of 5 μL/kg of placebo (saline) or 5 μL/kg of DMP or 10 μL/kg of DMP in 1:2:2 ratio. Patients who had at least 2 of 6 ventricular border segments classified as non-evaluable in either the apical 4- or 2-chamber view as determined by echocardiographic examination were eligible. Each patient was scheduled to undergo two baseline and two DMP or placebo echocardiographic imaging sessions (separated by a minimum of 30 minutes) at visit 1.

Efficacy objectives: As indicated in the study protocols, the primary and secondary objectives of these trials were to demonstrate that DMP 115:

Primary: • Improves left ventricular cavity (LVC) enhancement.

Secondary: • Improves endocardial border delineation (EBD).
• Improves videodensitometric measurements.

Study Hypothesis: No statistical hypothesis was stated in the protocol.

Sample Size: The sample size argument was based on cavity enhancement. A sample size of 80 was determined assuming 60% ventricular cavity enhancement in DMP 115 patients compared to 10% enhancement in placebo patients, to achieve 80% power using two-tailed test for proportions at 0.05 significance level.

Image acquisition: Echocardiographic examinations were performed in the following order:

(i) Baseline images were taken immediately prior to the first administration of DMP 115 or placebo followed by the post-injection images using the apical 4- or 2-chamber view that qualified the patient for the trial. Images were then recorded on a tape (Tape 1).

(ii) Following at least 30-minute period, step (i) was followed for a second baseline and post-injection images (Tape 2).

Image Evaluation: As planned in the protocol, the images were evaluated as follows:

(i) *Institutional Read*: At each site, the investigators viewed tape 1 and tape 2 as needed to determine cavity enhancement and endocardial border delineation. The investigators

evaluated change from baseline in the apical 4- or 2-chamber view that was used to qualify patient for the study.

(ii) *Blinded Read:* Three independent, blinded, and trained readers evaluated in random order the images of a single cardiac beat selected from the first imaging session (Tape 1) prepared blindly by a core laboratory personnel
LVC enhancement was read in paired format and EBD was read in unpaired format.

Endpoints: The primary and secondary endpoints for cardiac structure trials are summarized in Table 2.1.A

Table 2.1.A
Primary and Secondary endpoints for DMP 115 Cardiac Structure Trials (DMP 115-004 and DMP 115-005)

Endpoints	Scale	Comparison	Type of Evaluation	Comments
Primary:				
Left Ventricular Cavity Enhancement (LVCE)	0=No contrast 1= Weak contrast 2=Adequate contrast 3=Full enhanc. 9=Excessive contrast	Percent of subjects who had adequate to full LVCE compared to baseline image.	Paired	Excessive contrast was considered weak or no contrast.
Secondary:				
Endocardial Border Delineation (EBD)	0=Non-Evaluable 1=Evaluable 9=Not applicable (Seg. Not in image selected)	Percent of subjects who improved from non-evaluable to evaluable post-DMP.	Unpaired	EBD is not well-defined endpoint in these studies.
Videodensitometric volume at End-Diastole And End-Systole	Continuous	Mean change from baseline post-DMP injection 1.	Pre- and post	
Diagnostic Attributes:				
Ability to detect wall motion abnormalities	1=Impaired 2=Failed to impact 3=Improved	Percent of subjects improved at post-injection compared to baseline	Paired	

Source: Study Report for DMP 115-004 and DMP 115-005, vol. 139 and 146.

2.1.B Results

2.1.B.1 Patient Disposition and Characteristics

Patient Disposition: A total of 87 and 124 patients were randomized to treatment groups in study DMP 115-004 and DMP 115-005, respectively. Two patients (5 μL/kg of DMP group) in each study were either withdrawn due to misadministration of study drug or due to signs and symptoms after the first injection. Note that each patient was required to have both injections to be in the trial. The efficacy database excluded another patient in study –004 due to missing core laboratory evaluation for the blinded review. The efficacy data set included 85 patients in study –004 and 122 patients in study –005.

Protocol Deviations: Approximately 90% of the patients in both trials had at least one protocol violation. The most common violation was failure to obtain ECG or laboratory within the time period indicated in the protocol. First ECG was not obtained within 30 minutes of baseline and/or within 30 minutes of second injection in 76% and 72% of the patients in study –004 and study–005, respectively (source: Table 7, vol. 139 Clinical Study Report). This might have impacted the safety profiles (see MO's review).

Demographics and Baseline Disease History: The treatment groups appeared to be similar with respect to age, height, weight, race, and gender although, overall, the patients in study –004 was older compared to patients in study –005 (average age of 62.5 years vs. 53.1 years, respectively). Gender and ethnic distribution was approximately 4:1 in both studies (80% male vs. 20% female and 75-80% white vs. 20-25% others).

2.1.B.2 Primary Efficacy

Left Ventricular Cavity Enhancement (LVCE): Left Ventricular Cavity Enhancement (LVCE) was evaluated based on echocardiographic images from the first imaging session only. As mentioned in Table 2.1.B.2, the primary efficacy endpoint was the percent of patients who demonstrated adequate or full LVCE according to blinded, independent reader's evaluation. Table 2.1.B.2 below shows the efficacy results for both studies using blinded and unblinded reader's evaluation for the qualifying, apical 2- and 4-chamber views.

The sponsor used Fisher's exact test to examine the differences in LVCE between placebo and DMP 115 dose groups. Sponsor's finding were verified by the reviewer using the data sets provided in the NDA.

The analyses indicate that actual trial results were not consistent with what was assumed at the design stage. The sponsor assumed at the protocol stage a response rate (LVCE) of 60% and 10% for DMP 115 and placebo, respectively. But the trial results indicate that placebo (saline) had no response while DMP 5 μL/kg group had much higher response in study –004 than in study -005. Apparently the differences in LVCE between placebo group and the intended DMP 5 μL/kg

group were statistically more significant than what was expected according to any read (blinded or unblinded in both studies). In study –005, the LVCE was less than 60% according to two blinded reader's evaluation, yet the difference was statistically significant. Note that LVCE was evaluated in paired format, therefore, no separate baseline (pre DMP 115) score was recorded to independently validate whether baseline and placebo response was similar or not.

Table 2.1.B.2
Percent of patients with Ventricular Enhancement by Treatment groups, Read, and Views: Study DMP 115-004 and Study DMP 115-005

		Percent with Adequate or Full Cavity Enhancement		
Study #	Views	Placebo (n=18)	DMP 5 µL/kg (n=35)	DMP 10 µL/kg (n=33)
DMP 115-004	Qualifying* (Unblinded Read)	0%	91%	82%
	Qualifying (Blinded Read**)	0%	73-80%	60-63%
	Apical 2-chamber (Blinded Read)	0-5%	59-66%	57-67%
	Apical 4-chamber (Blinded Read)	0%	76-80%	57-60%
		(n=24)	(n=50)	(n=49)
DMP 115-005	Qualifying (Unblinded Read)	0%	84%	96%
	Qualifying (Blinded Read)	0%	28-73%	43-77%
	Apical 2-chamber (Blinded Read)	0%	20-56%	39-77%
	Apical 4-chamber (Blinded Read)	0%	32-72%	43-77%

* Views used to enroll patients in the trial.
* *Range for three blinded readers evaluation.

2.1.B.3 Secondary Efficacy

Endocardial Border Delineation (EBD): An improvement in EBD was defined as a non-evaluable segment prior to test drug (score of 0) that was evaluable after test drug (score of 1). Thus any segment changed from 0 to 1 after DMP or placebo, that patient demonstrated an improvement in EBD. Table 2.1.B.3 shows the percent of patients showing the improvement in EBD between placebo and DMP 115 dose groups. Overall, the improvement was higher for apical 4-chamber view than apical 2-chamber view. In study –004, improvement in EBD for both DMP doses were statistically significantly different from placebo according to 2 blinded evaluation, while in study-005, no statistically significant difference was noted according to any blinded evaluation.

In contrast to LVCE, where placebo had no effect, there appeared to be moderate placebo effect on EBD, although statistically not different from DMP 115 dose groups according to most blinded read. Therefore, the improvement in EBD in at least one segments for DMP dose groups compared to placebo was shown according to two readers evaluation in study –004, but similar evidence was not replicated according to any blinded readers evaluation in study –005.

Results of similar analysis for at least two segments were similar in both studies.

Table 2.1.B.3
Percent (%) of Patients showing Improvement in EBD in At Least One Segment by Study and Blinded Read.

Study #	Apical View	Placebo / 5 /10 µL/kg (p-value)		
		Reader 1	Reader 2	Reader 3
DMP 115-004	4-chamber	44/ 97/87 (p<.05)*	44/72/63 (NS)	35/79/82 (p<.05)*
	2-chamber	33/76/69 (p<.05)*	39/61/50 (NS)	40/55/54 (NS)
DMP 115-005	4-chamber	54/65/67 (NS)	64/76/82 (NS)	67/75/79 (NS)
	2-chamber	42/44/43 (NS)	52/54/63 (NS)	59/68/65 (NS)

* Significant difference from placebo for both doses.

Ventricular Videodensitometry: Videodensitometric measurements were made to quantify volumes in both apex and mid-chamber and both apical views at end-diastole and end-systole in the ventricular cavity. Table 2.1.B.4 shows the mean videodensitometric measurements at baseline and changes from baseline at End-Diastole. Mean changes for DMP dose groups were significantly higher compared to placebo in both regions, apical views in both studies. Similar results were noted at Mid-Systole and End-Systole.

Table 2.1.B.4
Videodensitometric Measurements (at End-Diastole) of Left Ventricular Enhancement – Change from baseline by Region and Apical Views: Study DMP 115-004 and DMP 115-005

		Apical 4-chamber View		Apical 2-Chamber View	
Study #/Regions	N	Baseline Mean(SD)	Change from Baseline Mean(SD)	Baseline Mean(SD)	Change from Baseline Mean(SD)
Study DMP 115-004:					
Apex					
Placebo	17	15.4(6.6)	3.8(8.5)	18.0(11.7)	2.4(12.4)
DMP 5 µL/kg	33	22.6(15.0)	15.8(16.4)*	20.7(14.4)	12.7(13.6)*
DMP 10 µL/kg	33	22.5(18.0)	19.1(17.3)*	22.7(18.0)	13.0(15.8)*
Mid-Chamber					
Placebo	17	13.2(6.2)	2.6(7.0)	15.3(7.3)	1.5(8.0)
DMP 5 µL/kg	33	18.7(13.1)	13.8(13.7)*	17.1(10.9)	12.8(14.3)*
DMP 10 µL/kg	33	19.1(15.7)	15.8(13.2)*	20.4(17.0)	11.8(13.1)*
Study DMP 115-005:					
Apex					
Placebo	24	26.0(21.5)	2.0(8.3)	27.8(19.8)	-0.7(10.1)
DMP 5 µL/kg	50	29.7(21.3)	14.4(14.5)*	28.3(20.5)	14.8(15.1)*
DMP 10 µL/kg	49	29.7(20.0)	23.5(21.5)*	27.5(19.2)	22.4(17.5)*
Mid-Chamber					
Placebo	24	20.5(17.3)	0.7(2.7)	21.0(16.5)	1.0(4.0)
DMP 5 µL/kg	50	24.0(18.0)	14.9(14.2)*	23.5(18.2)	15.3(17.3)*
DMP 10 µL/kg	49	23.8(15.8)	20.8(22.7)*	22.6(15.7)	20.1(18.6)*

*** Significantly different from placebo and from baseline (p<.05)**

2.1.C Reviewer's Comment on Efficacy

Two studies with identical but separate protocol were conducted in support of DMP 115 as a contrast agent in echocardiographic imaging. The objective of the trials were to demonstrate that echocardiographic imaging with DMP compared to placebo (saline) improves left ventricular cavity enhancement and border delineation in patients with suspected cardiac disease. Following study limitations noted in these trials, the strength and weaknesses of the efficacy summary are discussed below:

Limitations of the study design:

• One of the assumption made while sizing the studies at the protocol stage was that there would be 50% difference in cavity enhancement between DMP dose group and placebo (60% vs. 10%), when in fact the difference was much greater due to low or no response in placebo patients. With such a large difference between test product and the control, one would need only a few subjects to demonstrate statistical significance. Consequently, all comparisons between DMP 115 dose groups and placebo were statistically more significant than originally planned. Besides, statistical comparison against no response was not appropriate.

• The primary endpoint, i.e., cavity enhancement was blindly evaluated in paired format, without making separate evaluation for pre- and post-DMP images, which precluded any attempt to validate whether low cavity enhancement seen with saline was consistently similar to echocardiography alone. The secondary endpoint (EBD) was also not evaluated objectively to support the primary endpoint. It was defined as border improved if a patient had one segment evaluable after DMP 115 when the same segment was not evaluable at baseline. No other criteria were used to define EBD rather than simply stating that the patient was evaluable.

Strength/Weaknesses of the Evidence:

• According to sponsor's analyses, improvement in left ventricular cavity enhancement was significantly higher for post-DMP 115 patients compared to placebo patients in both study-004 and study-005. The proportion with improved cavity enhancement (in both apical chamber views) ranged from 60-80% in study -004 and 20-73% in study -005 (according to three blinded reader's evaluation), compared to 0% enhancement after placebo. In addition to inappropriate comparator, the efficacy of DMP 115 in cavity enhancement was further weakened by inconsistent results across studies.

• For endocardial border delineation (EBD), there was approximately 40-60% placebo response according to the same blinded reader's evaluation. The reason for such discrepancy between two endpoints in placebo patients was not clear. Despite significant inconsistency, the improvement in EBD evaluability was statistically significantly higher for DMP dose groups compared to placebo only in study –004 as per reader 1 and 3. None of the readers in study –005 indicated that DMP 115 was significantly better than placebo although they had seen more patients with evaluable segments after DMP 115 doses.

• All diagnostic attributes, i.e., , ability to detect wall motion abnormalities, determinations, appeared to be improved for DMP 115 patients as compared to placebo patients.

Given the testimonial nature of efficacy evaluation, lack of baseline information on cavity enhancement, inconsistency in efficacy findings across studies, the sponsor's statistical evidence in support of DMP 115 is <u>weak</u>.

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Based on the results and other pertinent information provided in the submission, following are the summary of efficacy in support of each purported indication:

Cardiac Indication:

• For the primary endpoint, i.e., ventricular cavity enhancement, the sponsor's claim of statistically significant improvement in cavity enhancement for DMP 5 µL/kg patients compared to placebo patients (28-80% *versus* 0%, range for three reader's evaluation) was not appropriate since no meaningful statistical comparison could be made with 0% response. The results were also dubious due to subjective nature of evaluation and potential for bias due to paired read. A valid comparison (at least baseline cavity enhancement) is needed to justify the efficacy of DMP 115.

• For the secondary endpoint, endocardial border delineation, a marginally statistically significant improvement was seen in one study but not supported by the results from the second study.

• For other secondary endpoint, endocardial border length, statistically significant impact of DMP 115 was noted for both apical 4- and 2-chamber view, although, results varied between reader's evaluation in both studies.

• For segmental wall motion evaluation, DMP 115 enhanced echocardiography permitted a higher percentages of matching segments with MRI than unenhanced images but the results could be biased since MRI itself is error-prone.

Due to the testimonial nature of the primary efficacy evaluation, lack of baseline information on cavity enhancement, use of inappropriate control, inconsistency in efficacy findings between similar trials, the sponsor's results from cardiac structure trials (DMP 115-004 and DMP 115-005) were weak. These trials do not demonstrate strong statistical evidence in support of DMP's ability in cavity enhancement but DMP appeared to improve videodensitometric measurements at both regions (apex and mid-chamber) and apical views consistently across both studies.

5.0 Recommendation

In the opinion of this reviewer, for cardiac indication, only endocardial border length outcomes did show some marginal evidence that DMP 115 enhances border in patient with cardiac abnormality.

/S/ 6/18/99

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